ITTREAT (Integrated Community Test - stage - TREAT) Hepatitis C service for people who use drugs: real world outcomes

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MOS data collection; AMJ statistical analysis; JJ, EP and HG: health economic analysis, HW: psychiatric expertise; SV: conceived original idea and wrote initial draft. All co-authors provided critical revisions and approved the final draft. SV is the submission's guarantor

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List of abbreviations
BBV blood borne viruses
DAA direct acting antivirals
HRQoL health related quality of life
HCV hepatitis C virus
IDU injecting drug use
ITTREAT Integrated Community-based Test - stage – TREAT
ITT intention to treat
mITT modified ITT
MDM multidisciplinary meeting
OAT opioid agonist treatment
PROM patient reported outcome measure
PEG INF pegylated interferon
PWUD people who use drugs
SF-12v2 Short Form 12 Health Survey
SFLDQoL Short form liver disease quality of life
SVR sustained virological response

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Abstract

Background/aims*:* Direct acting antivirals (DAA) provide an unprecedented opportunity for a "find-and-treat strategy". We aimed to report real-world clinical, patient reported and health economic outcomes of community-based HCV screening/treatment in people who use drugs (PWUD).

Methods: Project ITTREAT (2013-2021), established at a drug and alcohol treatment centre, offered a comprehensive service. Generic (SF-12v2 and EQ-5D-5L) and liver-specific (SFLDQoL) health related quality of life (HRQoL) were assessed before and after HCV treatment. Costs/case detected and cured were calculated. Primary outcome measure was sustained virological response (SVR) (intention to treat).

Results: Till March 2018, 573 individuals recruited, 462 (81%) males, mean age 40.5 ± 10.0 years. Of the 125 treated, 115 (92%) had past/current history of injecting drug use, 88 (70%) were receiving opioid agonist treatment and 50 (40%) were homeless. Twenty-six percent received interferon-based and 74% DAA-only regimens. SVR (ITT) was 87% (90% with DAAs). Service uptake/HCV treatment completion rates were > 95%, HCV reinfection being 2.63/100 person years (95% CI 0.67-10.33). HRQoL improved significantly at end of treatment in those with SVR: SFLDQoL (symptoms, memory, distress, loneliness, hopelessness, sleep and stigma) ($p</= 0.011$); SF-12 v2 physical and mental health domains ($p<0.001$); and EQ-5D-5L composite profile score ($p= 0.009$) and visual analogue scale, $p<0.001$. Cost (British pounds 2018) per case detected was £171; mean cost per cure (excluding medication) was £702 ± 188.

Conclusions: Excellent real-world SVRs in PWUD with significant improvement in HRQoL can be achieved at modest costs. Project ITTREAT endorses community-based integrated services to help achieve HCV elimination.

Key words: sustained virological response, patient reported outcomes, health economics, reinfection, HCV elimination

Lay Summary

1. Despite the new oral antiviral medication, achieving hepatitis C virus (HCV) elimination will require engaging with people who use drugs. However, such individuals often do not attend hospital appointments.
2. We describe a novel community-based model of care with all services being provided at a Drug and Alcohol Treatment Centre.
3. We observed excellent service uptake. HCV cure rates were comparable to a hospital- based service with significant improvement in quality of life. This was achieved at modest costs.
4. Such models of care need to be further researched at a national level

Introduction

Globally, hepatitis C virus (HCV) infection is a major health burden affecting about 71 million individuals (1). After the advent of direct acting antivirals (DAA) (2-6), the World Health Organisation (WHO) set ambitious targets to eliminate viral hepatitis by 2030 (1).

In England almost all HCV treatment (84%) occurs in secondary care (7). Of the estimated 113,000 with chronic HCV infection (8), injecting drug use (IDU) is cited as a risk factor in 92% (9). This is a marginalised/disenfranchised cohort with suboptimal engagement with health services (10). Nationally, while 50% with HCV being diagnosed by 2020 has probably been achieved, substantial work is needed to reach the 90% WHO target (1,8). Low treatment uptake amongst people who use drugs (PWUD) (<5-25/1000) (11) is a key factor hindering reduction in HCV disease burden. PWUD thus remain an important HCV reservoir impeding elimination.

A systematic review conducted for the National Institute for Health and Care Excellence in 2012 and 2017 found little published evidence of effectiveness for strategies to increase hepatitis case finding (12). The availability of DAA, however, provides an unprecedented opportunity for a paradigm shift in service delivery to a community “find and treat” strategy.

Though recent clinical trials and a meta- analysis confirm safety and efficacy of DAAs in PWUD (13-15), this may not reflect real world outcomes (15). Additionally, while HCV cure results in improved health related quality of life (HRQoL) (16-17), there are

limited data in PWUD, a cohort with significant comorbidity (18). Finally, without community-based HCV treatment cost estimates, making a future case for such a model will be difficult.

ITTREAT (**I**ntegrated Community-based Test - stage - TREAT) is a "one stop" HCV service set up at a large drug and alcohol treatment centre in South East England (19). Our aims were to collect real-world data relating to HCV screening and treatment and assess patient reported and health economic outcomes amongst those treated.

Patients and methods

Project ITTREAT, is an eight year study that commenced in December 2013 and here we present yearfour results (Dec 2013-Mar 2018). While clinical data is being collected throughout the study, an embedded study (Nov 2015-Mar 2018) included patient reported outcomes and a health economic analysis. Suppl file 1 shows the study design.

Study inclusion criteria were all adults aged ≥ 18 years attending the drug and alcohol treatment centre and willing and able to give informed consent. Exclusion criteria were unwilling to give informed consent. These individuals were still offered the service but their data were not collected.

The ITTREAT service, as described previously (19), involved an experienced hepatitis nurse working full time at the drug and alcohol treatment centre offering clients

blood borne virus (BBV) testing using the finger prick dry blood spot test (DBS) (Alere toxicology, London, UK) (20). This allowed assessment of HCV antibody (if positive reflex HCV qualitative RNA), hepatitis B surface antigen, hepatitis B core antibody and HIV antibody (20) using the following assays: Biorad hepatitis C antibody (ELISA), Murex hepatitis B surface antigen (ELISA), Biorad hepatitis B core total antibody (ELISA), Roche Cobas CAP CT HCV RNA (TAQ PCR BIORAD) and Gen Screen HIV Ultra (ELISA).

Those with a positive HCV qualitative RNA were called back to the drug and alcohol treatment centre and offered HCV quantitative RNA/genotype; clinical bloods; FibroScan®(402 Echosens); liver ultrasound and gastroscopy if cirrhotic (both performed at the local hospital) and HCV treatment assessment (Fig 1a).

After completion of these assessments, and consultation with the Hepatologist if necessary, the Hepatitis nurse presented clients at the weekly hospital multidisciplinary meeting (MDM) for treatment decisions.

DAAs became available in England in mid-2014 and HCV treatment is administrated via 22 national centers known as Operational Delivery networks (ODNs). DAA regimen was determined and funded by the National Health Service England (NHSE). Each ODN could only treat a pre-determined number of individuals per year. HCV treatment could be offered under exceptional criteria irrespective of fibrosis stage. This included PWUD who were eligible to receive DAA as a “window of opportunity” (21-22). Other barriers to HCV treatment included reluctance in treating PWUDs and

restriction on the number of DBS tests that could be performed per year at the drug and alcohol treatment centre. Therefore restrictions were not all related to NHSE and or fibrosis stage. Restrictions did ease over the study period, with each ODN treating an increasing number with HCV per year.

HCV treatment was delivered at the drug and alcohol treatment centre by the Hepatitis nurse under Hepatologist supervision. Clinics were “drop in”, with onsite psychiatric input, opioid agonist treatment (OAT), social/peer mentor support and a needle syringe programme. All those with a positive HCV RNA were deemed treatment eligible (irrespective of on going drug and alcohol use), unless not stable enough to engage and/or due to NHSE/other restrictions (deferred candidates, table 1).

Data collection

All data were prospectively collected by the Hepatitis nurse. Clinical data were collected between Dec 2013 - Mar 2018 (demographic, service uptake, HCV treatment compliance and outcomes). Patient reported outcome measures (PROMs) were collected in consecutive individuals (from Nov 2015 to Mar 2018), at start (pre) and at end of (post) DAA treatment utilising the Short Form 12 Health Survey (SF-12v2) (23), Short form liver disease quality of life (SFLDQoL) questionnaire (24) and EQ-5D-5L (25). Suppl file 2 provides details on how questionnaires were analysed and scored. Health economic data were collected from Nov 2015 to Mar 2018 in consecutive individuals undergoing DAA treatment. All steps in an individual’s care pathway (consultations, tests) from start of BBV screening to SVR testing were

recorded for inclusion in a micro costing exercise. Qualitative data have been reported separately (26).

Outcome measures

Primary outcome measure was intention to treat (ITT) sustained virological response (SVR) (SVR12 or SVR24 depending on regimen). Secondary outcome measures included service uptake (BBV screening, fibroscan, HCV treatment), HCV treatment completion rates and compliance; reinfection; changes in PROMs (generic and specific health related quality of life [HRQoL]), pre and post HCV treatment in those achieving SVR, cost per HCV case detected and cost per HCV cure for all those receiving DAA and for whom PROMs data were also collected.

Study definitions

PWUD: any history of current or past drug use (injecting or non-injecting) and or those currently receiving OAT

Current injecting and non-injecting drug use: use at time of HCV treatment initiation and or during HCV treatment.

Current alcohol use: use at time of HCV treatment initiation and or during HCV treatment.

Stability for HCV treatment: There were no strict definitions for stability. This was assessed on an individual basis by willingness and motivation to engage and be adherent with HCV treatment. Stability was determined, in the first instance by the Hepatitis nurse, in some cases with input from the clients themselves. In more

complex cases discussions were had with the Hepatologist, drug and alcohol team and colleagues at the Liver MDM.

SVR: absence of detectable virus (at any level) 12 or 24 weeks after end of treatment (EOT).

Reinfection: any level of detectable virus after achievement of SVR. This was assessed 48-60 weeks post SVR as stipulated by NHSE. ODNs incurred financial penalties for failure to collect this data.

Cirrhosis (Metavir F4): liver stiffness measurement (LSM) $\geq$ 12 kPa (27-28).

Homeless: street homeless/living in temporary accommodation.

ITT analysis: Included all those commencing HCV treatment.

Modified ITT (mITT) analysis: Excluded those lost to follow up after commencing HCV treatment.

Statistical analysis

Clinical data (all those recruited from Dec 2013 – March 2018)

Data are summarised using counts, means $\pm$standard deviations, medians (interquartile ranges [IQR]), or percentages. Student's t-test and Chi-Square test were utilised for continuous and categorical variable respectively. Logistic regression analysis was used to model the relationship between the binary dependent outcomes (0 vs.1) treatment uptake (treated vs. deferred) and treatment outcome (SVR vs. non-SVR), and key independent factors (age, gender, IDU (current/past), , current non-IDU, alcohol use (current/past), current alcohol, use receiving OAT, homeless at initial assessment, any psychiatric diagnosis and fibrosis stage). A multivariate logistic regression model was then derived to look at the relationship

between the key factors and the dependent outcome. To build the model, the statistically significant key factors from the bivariate analyses were added to the null model using forward selection where the factor with the highest significant p-value ($p < 0.05$), based on the likelihood ratio test, was added next. Factors were removed from the model if $p > 0.1$.

HCV reinfection rate was calculated in those who had achieved SVR as the number of reinfections observed in the study period divided by the sum of all the years each individual was observed for multiplied by 100. The rate was presented per 100 person years (PY).

PROM analysis (consecutive individuals receiving HCV treatment from Nov 2015-Mar 2018)

Differences in pre and post HCV treatment scores were calculated (mean ± standard deviation) and compared using paired Student's t-test. For each PROM, scores with <50% missing were imputed. Data were assumed to be missing at random. PROMS meeting the data completeness criteria were entered into the imputation model, which used chained equations, auxiliary variables (age, gender, whether current IDU and whether homeless at initial assessment) and 20 imputations (29). A sensitivity analysis was carried out by establishing whether the conclusions from the imputation model differed to those from a complete case analysis. For all statistical analysis a p-value < 0.05 was considered significant and the software used was STATA v13.

Health economic analysis

A cost was attributed to staff time spent in consultations based on nationally validated rates, in British pounds 2018 (30). Costs of tests were obtained from local financial managers.

Cost per case detected was calculated as the total cost of all professional time and tests performed, involving all those invited to be screened, divided by the total number of individuals with a positive HCV qualitative RNA (a case), over the total study period (Dec 2013 to Mar 2018).

To calculate the cost per cure of those receiving DAA (Nov 2015 to Mar 2018), the total cost of assessments and treatments was calculated at the individual level. Average costs were compared between those achieving SVR and those who did not, and between those receiving DAA + pegylated interferon vs. DAA-only regimens. Costs of medications, and time spent by the nurse in preparing documents, and presenting cases at the hospital MDM were not included.

A macro level cost analysis was undertaken at the level of the service, based on the full economic cost of employing a nurse for a period of a year.

Ethical approval for the study was obtained from NRES Committee East Midlands - Derby (REC ref 13/EM/0275), all participants signing an informed consent.

Results

Service uptake and case detection

Table 1 shows baseline clinical and demographic data and service uptake, stratified by whether treated or HCV treatment deferred. Of the 558 tested, 259 (46%) were HCV qualitative RNA positive, this being significantly higher in those with history vs. no history of IDU (60% vs. 13%, p<0.001).

Assessment

The 259 with a positive HCV RNA underwent further assessment (Fig 1a and suppl Fig 1) including a community based-fibroscan. Overall 47% (104/219) of those undergoing a fibroscan had >F2 fibrosis and 24% (53/219) had cirrhosis.

Treatment was deferred in 134/259 (53%) with a positive HCV RNA (table 1); 80 (31%) were not stable enough and 54 (21%) due to NHSE and other restrictions. Of those stable to receive HCV treatment (n=179), 125 (70%) have been treated until March 2018. Table 2 shows bivariate and multivariate analysis of factors associated with receiving HCV treatment vs. treatment being deferred. Independent predictors of receiving treatment were absence of current IDU (OR 0.39, 95% CI 0.25-0.72, p=0.002) and absence of homelessness (OR 0.40, 95% CI 0.24-0.66, p=0.001).

HCV treatment outcomes

Table 1 shows baseline data in the 125 individuals who received HCV treatment. Prevalence of current IDU, alcohol use, receiving OAT and homelessness at initial

assessment were 34%, 26%, 70% and 40% respectively, genotype distribution (1 vs. 3) was 45% vs. 49%. Just over a third (34%) had cirrhosis (table 1).

Overall, 33/125 (26%) received interferon-based and 92 (74.0%) DAA-only regimens, (sofosbuvir-based in 48/92,52%) (suppl table 1). Overall, 71% (89/125) of the regimens contained ribavirin. From 2014-2016, 28 received DAA-only regimens (included 11% with F0-F1 fibrosis) but due to easing of NHSE and other restrictions, this increased to 64 from 2017-2018 (included 48% with F0-F1 fibrosis).

On an ITT analysis SVR was 87% overall and 90% (83/92) in those receiving DAA-only regimens (fig 1b). Of the 16 with non-SVR, nine were true virological failures with seven (6%) being lost to follow (suppl table 1). Excluding these seven, on a mITT analysis, overall SVR was 92% and 95% in those receiving DAA-only regimens (Fig 1b).

Table 3 shows demographic and clinical data in those with and without SVR. SVR was 79% (34/43) if current IDU. Logistic regression of non-SVR was carried out on age, current IDU and treatment regimen (DAA-only vs. pegylated interferon/ribavirin + DAA). Insufficient data prevented statistical analyses of other variables. Current IDU was associated with an increased risk of non-SVR (OR=3.84, 95% CI 1.29-11.4, p=0.016). There was no association with age (OR=0.98, 95% CI 0.93-1.04; p=0.598) or regimen (OR-2.48, 95% CI 0.84-7.32), p=0.099).

In those individuals who were offered HCV treatment (n=125), uptake was 100% and treatment completion rate was 98% (122/125). Of the total of 406 community treatment clinic sessions, 96% (389) were attended.

Reinfection

Up to March 2018, of the 109 individuals achieving SVR, 76 have been retested, of whom two (3%) have developed HCV reinfection (2.63/100 PY, 95% CI 0.67-10.33). Both had IDU relapse. Reinfection data are currently unavailable in the remaining 33 individuals.

Patient reported outcome measures (PROM)

During Dec 2015 to Mar 2018, 85 consecutive individuals were offered and accepted questionnaire-based assessments pre and post HCV treatment. Twelve received pegylated interferon/ribavirin + sofosbuvir and 73 DAAs-only, 61/85 (72%) of the regimens contained ribavirin. Of the 85, 78 (92%) achieved SVR. Of the seven not achieving SVR, five received DAA-only regimens and two pegylated interferon/ ribavirin + sofosbuvir. Of the 78 achieving SVR, 29% (23/78) were current IDUs, 27% (21/78) were current non-IDUs and 4% (3/78) were both current IDUs and non-IDUs.

Two domains of SFLDQoL (sex and effect of liver disease) had >50% missing data and so were excluded from the imputation model and were only summarised using complete cases (sex n=8; effect of disease n= 17). Remaining PROMs had 18-22% pre – post scores missing and 303 imputations were made.

Figs 1c and 1d show the mean changes in SF-12v2 and SFLDQoL scores respectively, pre and post HCV treatment in the 78 who achieved SVR. Actual scores are shown in suppl table 2. There were significant improvements ($p<0.05$) in all domains tested. Sensitivity analysis showed that there was no change in drawn conclusions as a result of multiple imputation following a complete case analysis (data not shown). Compared to baseline, there were also significant improvement in EQ-5D-5L scores at the end of HCV treatment: composite profile score 0.65 $\pm$ 0.3 vs. 0.73 $\pm$ 0.03, $p=0.009$ and VAS 52.79 $\pm$ 2.04 vs. 72.89 $\pm$ 1.59, $p<0.001$.

Health economic outcomes

Cost per case detected*:* During the full study period (Dec 2013 to March 2018) a total of 573 individuals were invited for screening of which 558 accepted and 323 had positive HCV antibody. Of the 323 individuals with positive HCV antibody, 259 had a positive qualitative HCV RNA, with a cost per case detected of £171 (table 4)

Cost per cure*:* Data on service utilisation were collected from 85 individuals who received interferon + DAA (n=12) or DAA-only regimens (n=73) between November 2015 and March 2018. The consultations and tests received by this subgroup, and associated costs are shown in table 5. The overall mean cost per cure (excluding drug costs) was £702 $\pm$ 188. Average costs were lower for individuals who did not achieve SVR and higher for those receiving interferon + DAA regimens. Costs broken down into the pre-treatment, treatment and follow up phases are shown in suppl table 3.

The annual cost of running the service, based on the full economic cost of a band 7 nurse (inclusive of management and facilities overheads) was around £84,000 (British pounds 2018).

Discussion

Our real-world prospective community HCV study in PWUD is novel as in addition to assessing SVR, it also provides data on patient reported and health economic outcomes. Our treated cohort had high prevalence of current/past IDU (92%) and alcohol (89%) use with 70% on OAT and 40% being homeless. Despite this, service uptake and HCV treatment completion were close to 100% with an almost 90% SVR. Three validated and independent HRQoL indicators confirmed significant improvement in generic and liver specific HRQOL at end of HCV treatment, achieved at modest costs. Importantly, though initially funded by research grants, our favourable outcomes indicated sustainability, leading to the adoption of the service by the hospital trust.

We attribute the success of ITTREAT to it being a “one-stop” integrated and non-judgmental service, which helped mitigate against non-engagement, corroborated by our qualitative data (26) and a recent systematic review (31). The Hepatitis nurse effectively linked all the different components of the service. In contrast, prior to set up of ITTREAT, only 5% of individuals with HCV infection referred from our drug alcohol treatment centre attended their local hospital appointment, none eventually being treated (10).

Our data is consistent with a recent meta-analysis in PWUD (15) (approximately 50% of the studies being community –based), that reported treatment completion rates of ~97% with SVR amongst those on OAT and recent IDU/non-injecting use being 90·7% (95% CI 88·5-93·0) and 87.7% (95% CI 84.2%-91.3%) respectively.

Our community-based ITT SVR with DAAs (~90%) are similar to clinical trials involving PWUD (91.5%-94%) (13-14), but lower than that observed in non-PWUD clinical trials (4-5) and real world studies (96%- 99%) (3,6). However our mITT SVR (95%) are comparable suggesting that the apparently lower SVR in PWUD is probably due to loss to follow up rather than true virological failures. Our 6% loss to follow up (consistent with the aforementioned meta-analysis [15]) is indeed higher than that seen in non-PWUD real world studies and clinical trials (<1%) (4,6). A recent randomised controlled trial in PWUD on OAT, found higher SVR in those receiving group or directly observed treatment (94%-98%) compared with self-administered DAA therapy (90%). This highlights potential strategies for increasing treatment retention amongst PWUD (32).

Our lowest SVR were seen in those with current IDU (79%). This is consistent with the Iceland TRAP C study (SVR 82%) (33), where even after accounting for the high (15%) dropouts, SVR was lower in those with IDU vs. no IDU in last six months (89.9% vs. 95.3%) (33). This should however not deter health care professionals from offering HCV treatment to people with recent IDU. Mathematical modelling suggests that with an 18 fold increase in HCV treatment (54/1000 PWUD/ year), and assuming a 90% SVR, HCV seroprevalence can be reduced by 75% (to <15% within 15 years).

An 80% SVR will only reduce impact by 12%-15%, still adequate for a treatment as prevention strategy (34). PWUD should therefore be a priority for scaling up HCV testing/treatment and linkage to care (15).

Our HCV reinfection rate of 2.6/100 PY is supported by recent data (35-36). In Rossi et al's study (36), reinfection amongst recent and former PWUD was 3.1/100 PYs (95% CI 1.9-23.5) and 1.4/100 PYs (95% CI 1.1-12.9) respectively, with only one individual receiving daily OAT developing reinfection. This reiterates the importance of on-going follow up of PWUD post SVR to ensure engagement with OAT services

Earlier studies (summarised in two recent reviews [16-17]) report the severe HRQoL impairment with interferon-based treatments; persisting for up to 12 weeks post treatment irrespective of SVR. Ribavirin was also associated with modest but reversible impairment (16-17). DAA on the contrary significantly improve patient reported outcomes (irrespective of fibrosis stage), within the first month into treatment (16-17). Our study suggests that even in PWUD, a cohort with considerable comorbidity (18), successful DAA therapy results in significant improvements in generic and liver specific HRQOL. This could have also contributed to adherence. Therefore in PWUD, DAA associated virological cure results in benefits over and above that related to just the liver. An Australian study reported that PWUD are seeking outcomes 'beyond cure' including improved physical and mental health and positive changes in identity and social relationships (37).

Our excellent outcomes in this hard-to-reach group have been achieved at modest cost (~ £880, at 2018 prices), when screening, assessment, and treatment were combined. Drug costs, which make up a large proportion of treatment costs were excluded since these vary depending on local negotiations, and are expected to fall over time. Prior studies (38) have recorded higher costs per cure, even after medication costs were discounted. These studies, however, are not directly comparable with ours since they were based on the earlier treatment regimens where adverse events and treatment non-compliance were more common (38).

Our study did have limitations. This community model of care was based at a single site in England, the trusting client provider relationship being the key to engagement (26). Since this may not be applicable to other geographical sites our study lacks generalisability and external validity to support a national change in service delivery. However, a recent systematic review, involving studies from multiple countries reporting different models of care reported excellent community-based SVR in PWUD (15).

In conclusion Project ITTREAT endorses community-based integrated services. Excellent real-world SVR in PWUD can be achieved at modest costs with significant improvement in HRQoL after HCV cure. Such models of care could help pave the way for HCV elimination.

Figure legends

Fig 1a. Participant pathway (with numbers at each stage)

Fig 1b. SVR in treated cohort

Fig 1c. Mean (with SE bars) SF-12 scores pre and at end of (post) HCV treatment in those achieving SVR (n=78)

Fig 1d. Mean (with SE bars) SFLDQoL scores pre and end of (post) HCV treatment in those achieving SVR (n=78)

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Table 1 Baseline data in whole cohort and in those with a positive HCV RNA

		HCV RNA positive n=259	
	Whole cohort (n=573)	Deferred cohort (n=134)	Treated cohort (n=125)
Age	40.5 ±10.0	40.9 ±9.6	45.1±9.1
Age ≤ 40	290 (51%)	64 (48%)	40 (32%)
Age ≥ 60	21 (4%)	6 (5%)	9 (7%)
Gender			
Male	462 (81%)	110 (82%)	102 (82%)
Ethnicity			
White British	523 (91%)	122 (91%)	114 (91%)
Sexual orientation (n=569)			
Heterosexual	539 (95%)	129 (96%)	113 (92%)
Injecting drug use (current/past)			
Yes	411 (72%)	123 (92%)	115 (92%)
No	162 (28%)	11 (8%)	10 (8%)
Current injecting drug use			
Yes	178 (31%)	65 (49%)	42 (34%)
No	395 (69%)	69 (52%)	83 (66%)
Injected Drugs used			
Heroin	174 (30%)	63 (47%)	34 (27%)
Cocaine	74 (13%)	35 (26%)	29 (23%)
Others	4 (1%)	0 (0.0%)	23 (18%)
Currently Injecting daily	*	*	15 (12%)
Non Injecting drug use			
Current non injecting drug use	224 (39%)	55 (41%)	38 (30%)
Non-injected drugs used			
Heroin	75 (13%)	18 (13%)	8 (6%)
Cocaine	76 (13%)	15 (11%)	11 (9%)
Others	142 (25%)	33 (25%)	23 (18%)
Daily use	*	*	23 (18%)
Alcohol use (current/past)	505 (88%)	124 (93%)	111 (89%)
Current alcohol use	214 (37%)	63 (47%)	32 (26%)
Drinking >21 units/week	134 (23%)	40 (30%)	25 (25%)
Homeless at initial assessment	289 (50%)	79 (59%)	50 (40%)
Receiving OAT	299 (52%)	96 (72%)	88 (70%)
Any psychiatric diagnosis	288 (50%)	86 (64%)	81 (65%)
Uptake of BBV testing	558/573 (97%)		
HBcAb positive	95 (17%)	35 (26%)	33 (26%)
HCV Ab positive	323 (58%)		
HCV RNA positive	259/323 (80%)		
Underwent genotyping	241/254 (95%)	118 (88%)	123 (98%)
1	2 (1%)	0 (0%)	2 (2%)
1a	111 (46%)	61 (52%)	50 (41%)
1b	5 (2%)	2 (2%)	3 (2%)
3	111 (46%)	51 (43%)	60 (49%)
Other	12 (5%)	4 (3%)	8 (7%)
Underwent HCV viral load	244/254 (96%)	119 (89%)	125 (100%)

Viral load (iu/L) **Viral load > 1.0 x 10^6 (iu/L)**	1.3 x 10^6 ±2.2 x 10^6 89 (32%)	1.2 x 10^6 ±1.9 x 10^6 35 (29%)	1.9 x 10^6 ±3.1 x 10^6 54 (43%)
Comorbidity	147 (10%)	43 (32%)	51 (41%)
Underwent fibroscan*	220/254** (87%)	95 (74%)	124 (99%)
F0-F1 (<7.1 kPa)	115 (53%)	64 (67%)	51 (41%)
F2-F3 (> 7.1-11.9 kPa)	51 (22%)	20 (21%)	31 (25%)
F4 (≥ 12 kpa)	53 (24%)	11 (12%)	42 (34%)
Bilirubin (μmol/L)	7(5) [n=277]	7 (5) [n=104]	8 (6)
ALT (iu/L)	52(55) [n=277]	55 (67) [n=104]	57 (48)
Albumin (g/L)	45.0 ±5.4 [n=277]	45.4 ±5.4 [n=104]	44.3 ±4.8
INR	1 (0.1) [n=204)	1 (0.1) [n=61]	1 (0.1)
Platelets (10^9/L)	206.2 ± 68.5 [n=232]	228.3 ± 70.5 [n=84]	190.9 ± 63.6
Received prior HCV treatment	13 (2%)	2 (2%)	8 (6%)

OAT Opioid agonist treatment

* Reference no 27-28

** Fibroscan unsuccessful in one

Brackets [] indicate number with data available

Normal values: bilirubin 0-21 μmol/L, ALT 0-41 iu/L, albumin 35-52g/L, INR 0.8-1.2, platelets 150-450x10^9/L

Table 2. Bivariate and multivariate analysis of those who received HCV treatment vs. those in whom treatment was deferred

	Bivariate analysis			Multivariate analysis		
Key variables	OR	95% CI	p-value	OR	95% CI	p-value
Age (per year increase in age)	1.05	(1.02, 1.07)	0.001			
Male	1.03	(0.54, 1.94)	0.943			
IDU (current/past)	1.04	(0.42, 2.53)	0.936			
Current IDU	0.39	(0.23, 0.66)	<0.001	0.42	(0.25,0.72)	0.002
Current non-IDU	0.69	(0.42, 1.15)	0.156			
Alcohol use (current/past)	0.65	(0.28, 1.51)	0.313			
Currently drinking alcohol	0.54	(0.33, 0.9)	0.018			
Receiving OAT	0.63	(0.37, 1.06)	0.079			
Homeless at initial assessment	0.40	(0.24, 0.66)	<0.001	0.43	(0.26, 0.72)	0.001
Any psychiatric diagnosis	1.02	(0.62, 1.69)	0.939			
F2-F4 fibrosis	1.32	(0.81, 2.17)	0.260			

Bases for all categorical variables are the 'no' category

Table 3 Baseline demographic and clinical data in those with SVR and non-SVR (n=125)

	Non- SVR n = 16	**SVR n = 109**
Age (yrs)	44.0 ±8.4	45.2 ±9.2
Age ≤ 40	8 (50%)	32 (29%)
Age ≥ 60	0 (0%)	9 (8%)
Gender		
Female	0 (0%)	23 (21%)
Male	16 (100%)	86 (79%)
Injecting drug use (current/past)	16 (100%)	99 (91%)
Current injecting drug use	9 (56%)	33 (30%)
Injecting daily§	5 (31%)	10 (9%)
Injecting less than daily§	4 (25%)	23 (21%)
Current non injecting drug use	5 (31%)	33 (30%)
Using daily**	4 (25%)	19 (17%)
Using less than daily §	1(6%)	14(13%)
Alcohol use (current/past)	15 (94%)	96 (88%)
Current alcohol use	5 (31%)	27 (25%)
Currently drinking > 21 units/wk §	4 (25%)	21 (19%)
Homeless at initial assessment	6 (38%)	44 (40%)
Receiving OAT	12 (75%)	76 (70%)
Psychiatric diagnoses	10 (63%)	71 (65%)
Genotype 1	8 (50%)	47 (43%)
Genotype 3	7 (44%)	53 (49%)
Viral load (VL)	$1.8x10^6$ ±$2.6x10^6$	$1.9x10^6$ ±$3.2 x10^6$
VL > 1,000,000 iu/L	8 (50%)	45 (42%)
Comorbidity	8 (50%)	43 (39%)
Liver stiffness measurement ≥12kPa	5 (31%)	37(34%)
APRI ≥ 2	3 (19%)	11 (10%)
Bilirubin (mmol/L)	8.5 (5.5)	8 (6.0)
ALT (iu/L)	59 (76)	56.5 (47)
Albumin (g/L)	44.4 ±4.5	44.3 ±4.8
INR	1.0 (0.1)	1.0 (0.1)
Platelet count (10^9/L	176.2 ±58.0	193.7±63.5
Regimen		
DAA-only	9 (56%)	83 (76%)
PEG INF/RBV ± DAA	7 (44%)	26 (24%)

Note: §= proportion calculated out of the subset who report current drug/alcohol use; for continuous variables data presented as mean ± sd for normally distributed or median (IQR) for skewed data respectively

Table 4. Cost per case detected for 573 individuals invited for blood borne virus screening

Item	Time per person (minutes)	Number of individuals	Unit cost[+]	Cost per person	Total cost £ 2018
Initial invitation for BBV screening screen by substance use worker	5 minutes	573	£51/hour	£4	£2435
Initial consultation with nurse for	15 minutes	558	£53	£13	£7394
Lab test HCV antibody positive in DBS	Not relevant	558	£33[++]	£33	£18414
Lab test qualitative HCV RNA (from same DBS if HCV antibody +ve)	Not relevant	323	£50	£50	£16150
Number of cases (positive qualitative HCV RNA), cost per case, total screening costs		259		£171	£44,393

[+] Unit costs: Alcohol health worker/ liaison nurse/ substance misuse worker, Curtis and Burns 2018, page 50; Band 7 nurse, Curtis and Burns 2018, page 119; costs of tests from local financial managers.
[++] Cost of DBS for initial BBV screen

Table 5 Cost per cure (British pounds, 2018) in 85 individuals receiving direct acting antivirals (excludes cost of drugs)

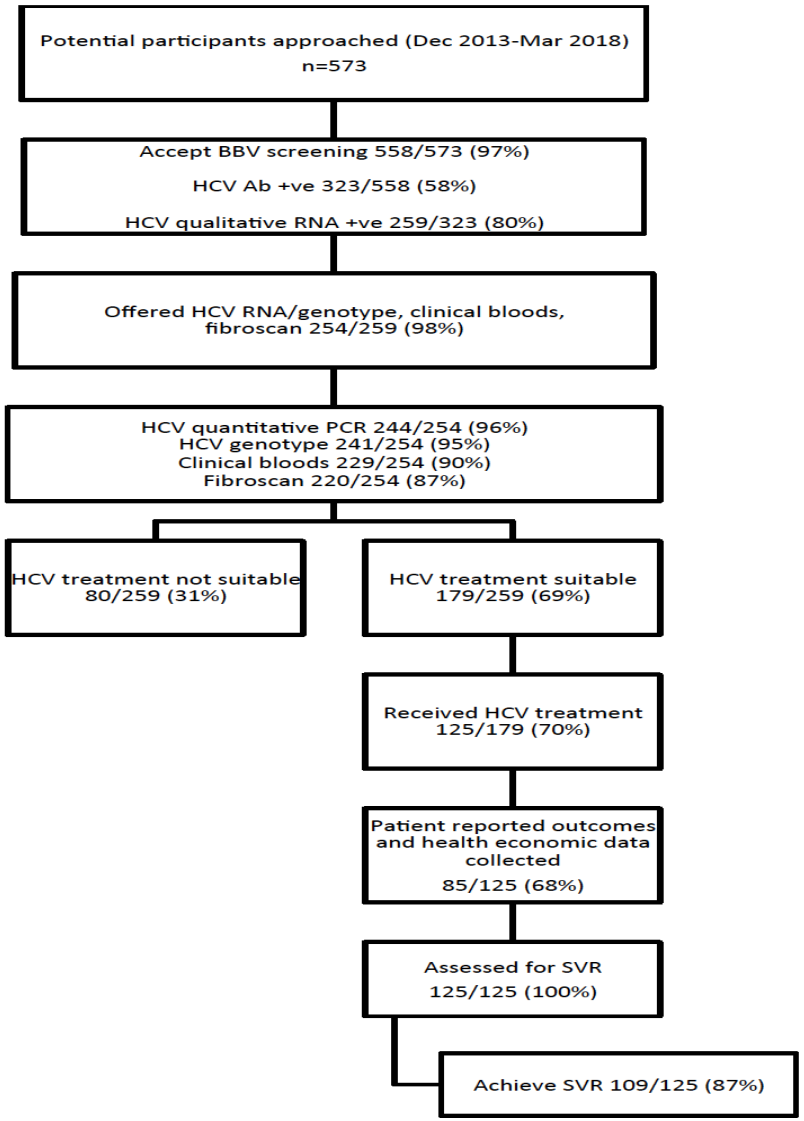
Items of service use	Number of tests and consultations[1]					Costs (£ 2018)[6]			
	Total	Mean	SD	Min	Max	Mean	SD	Min	Max
Quantitative HCV RNA[2]	253	3.0	0.2	2	3	207	10.6	139	208
Full Blood Count(FBC)[2]	253	3.0	0.2	2	3	29	1.5	19	29
Blood Renal Profile(U/E)[2]	253	3.0	0.2	2	3	13	0.7	9	13
Blood Liver Function Test(LFT)[2]	253	3.0	0.2	2	3	16	0.8	11	17
Nurse consultation brief (30 mins)[3]	513	6.0	2.5	2	17	160	66.1	53	451
Nurse consultation (60 mins)	91	1.1	1.1	0	7	57	56.5	0	371
Hepatologist review (30 mins)	10	0.1	0.3	0	1	6	17.5	0	54
Nurse home visit (30 mins)	44	0.5	2.2	0	15	15	63.8	0	443
Fibroscan[4]	84	1.0	0.1	0	1	124	13.6	0	125
Liver ultrasound (hospital) [5]	63	0.7	1.3	0	6	74	125.5	0	600
Granulocyte colony stimulating factor Test (GSCF)	3	0.04	0.3	0	3	2	17.2	0	158
Costs	85					702	188	456	1,349

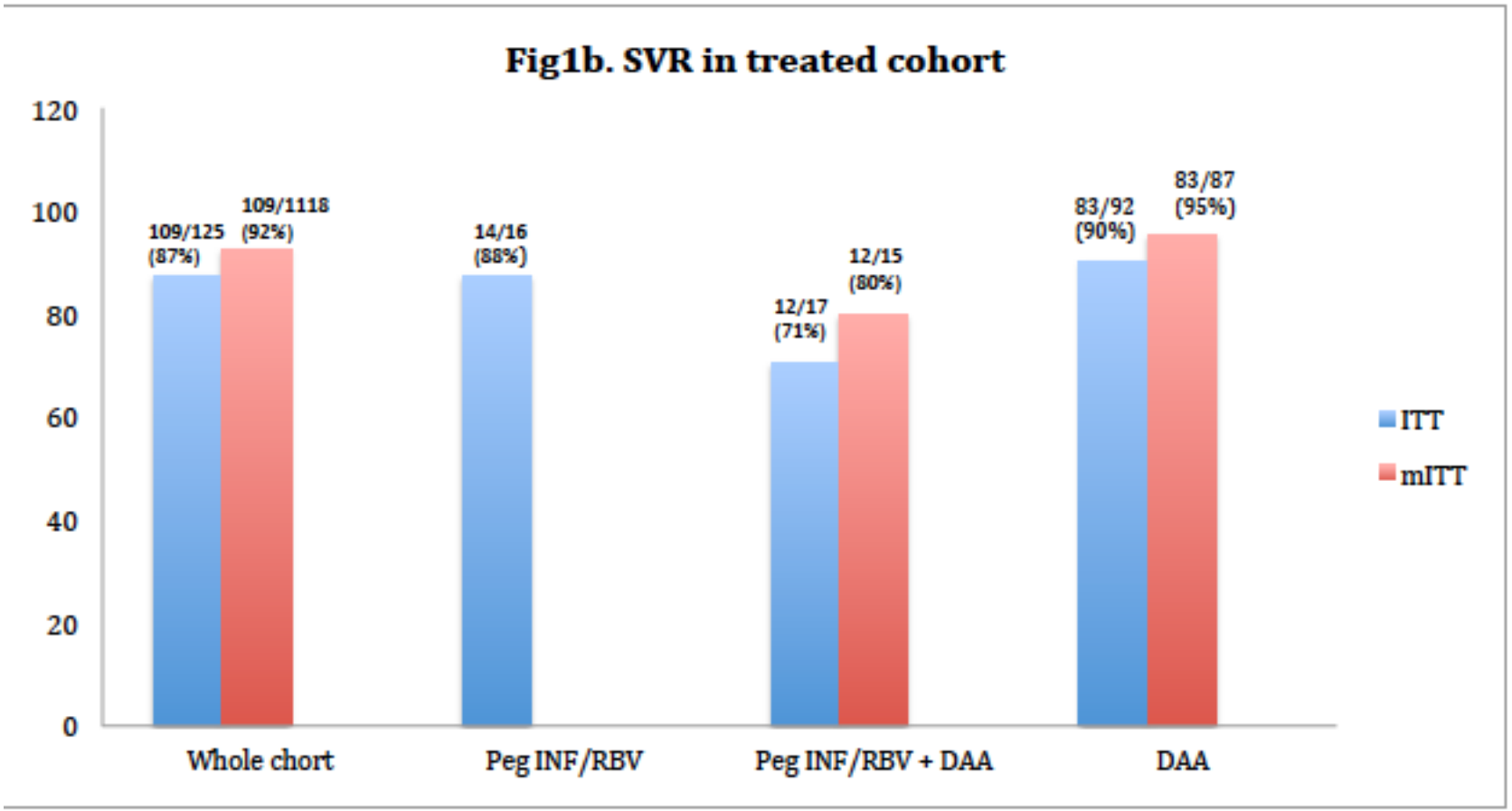
Subgroup comparisons	N	Mean	SD	Min	Max
Achieved SVR	78	709	193.3	505	1349
Did not achieve SVR	7	621	83.7	456	709
DAA-only regimen	73	684	161.6	505	1136
DAA with PEG INF	12	814	288.3	456	1349
SVR with DAA-only regimen	68	685	167.2	505	1136
Non SVR with DAA-only regimen	5	663	31.6	630	709
SVR with DAA + PEG INF/RBV regimen	10	874	277.5	603	1349
Non SVR with DAA + PEG INF/RBV regimen	2	516	85.8	456	577

[1] Tests/consultations during three phases: pre-treatment, treatment, 12 or 24 weeks post treatment. One patient died just after completing HCV treatment

[2] Since blood test frequency changed during the study period, we assumed that all patients received one set of blood tests (Quantitative HCV RNA, FBC, U/E and LFT) in each of the three phases (as was the protocol at the end of the study).
[3] Consultations data missing for some patients so one 30 minute nurse consultation was assumed.
[4] Every patient except 1 received a Fibroscan pre-treatment.
[5] Only patients with F4 Fibrosis received ultrasounds pre-treatment, during treatment and during follow up.
[6] Unit costs: Costs of tests from the local financial manager: quantitative HCV RNA £69.41; FBC £9.58; U/E £4.32; LFT £5.50; Fibroscan £125; liver ultrasound £100; GCSF £52.70. Band 7 nurse £53 per hour, Curtis and Burns 2018, page 119 with £3 added for travel costs for home visits; Hepatologist £108 per hour, Curtis and Burns 2018, section 15.
DAA direct acting antiviral, PEG INF pegylated interferon, RBV ribavirin

Fig 1a. Participant pathway





Peg INF pegylated interferon; RBV ribavirin; DAA direct acting antivirals; ITT intention to treat; mITT modified intention to treat

Hhhh

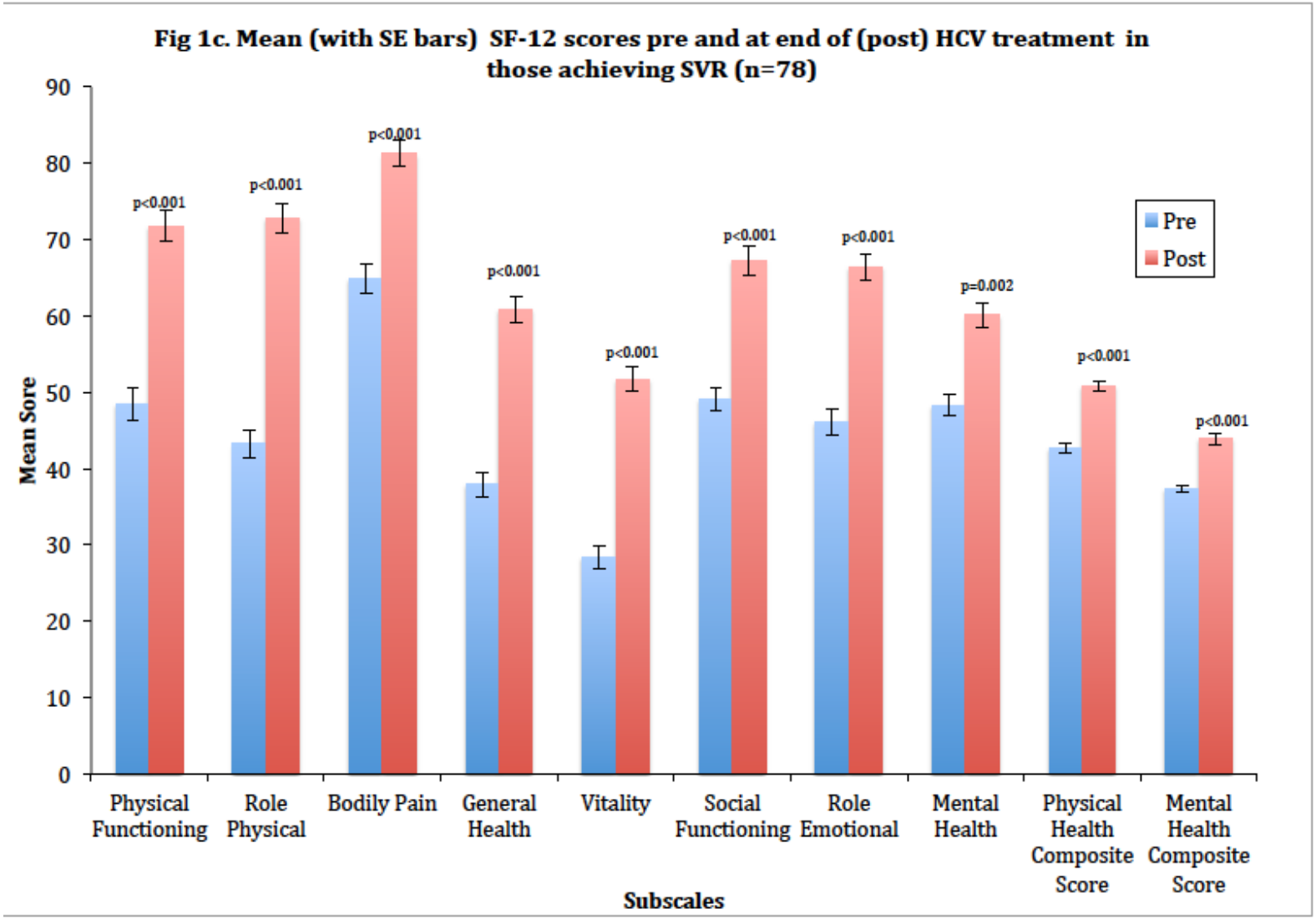
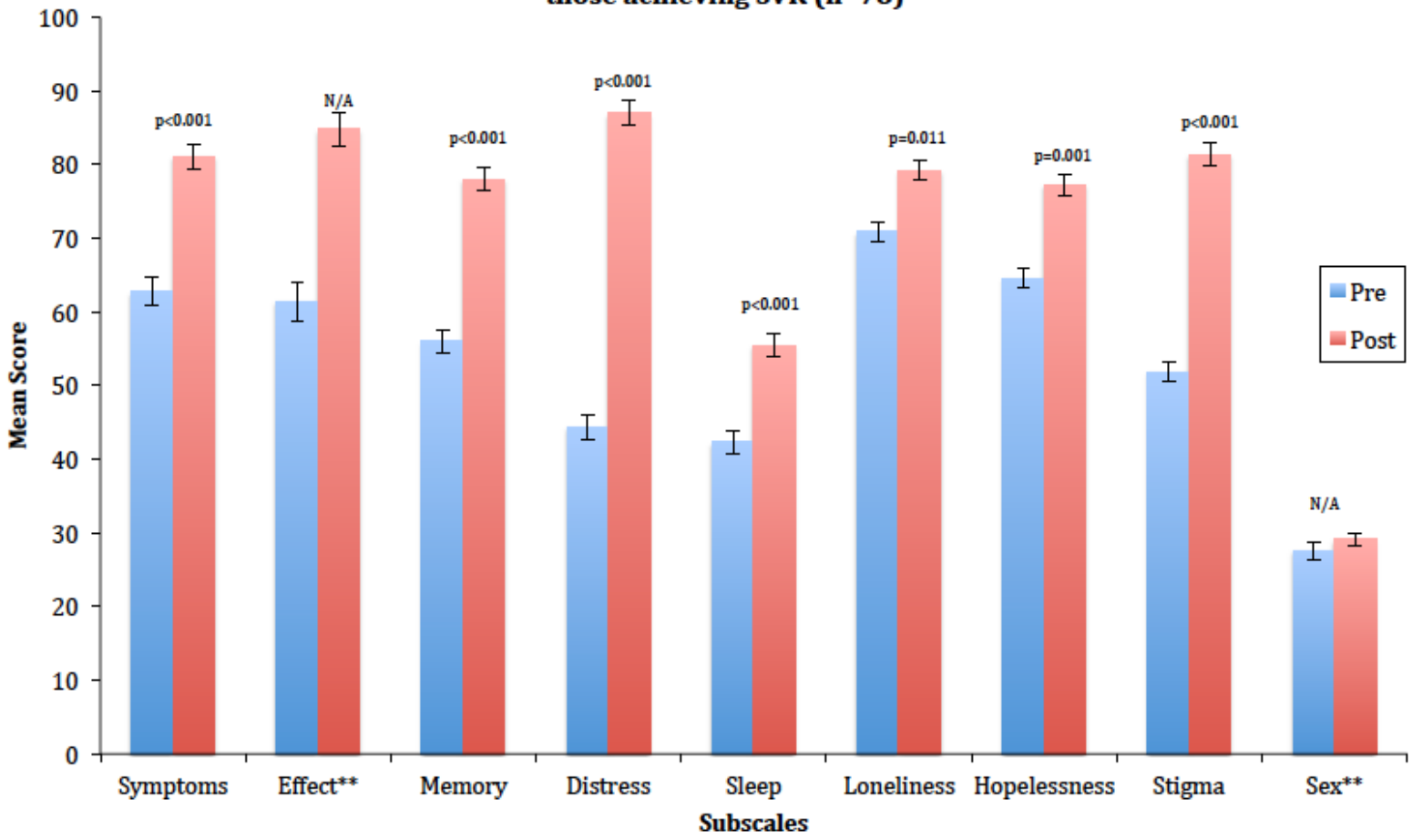


Fig 1c. Mean (with SE bars) SF-12 scores pre and at end of (post) HCV treatment in those achieving SVR (n=78)
Mean Sore
90
80
70
60
50
40
30
20
10
0
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p<0.001
p=0.002
p<0.001
p<0.001
Pre
Post
Physical Functioning
Role Physical
Bodily Pain
General Health
Vitality
Social Functioning
Role Emotional
Mental Health
Physical Health Composite Score
Mental Health Composite Score
Subscales

Fig 1d. Mean (with SE bars) SFLDQoL scores pre and end of (post) HCV treatment in those achieving SVR (n=78)



** PROM has missing data level above the threshold and a small count and so is excluded from statistical comparison analysis